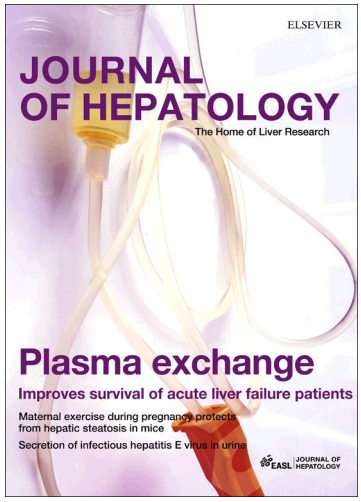

Letter to the Editor

Reply to «Lack of evidence of an effect of Direct Acting Antivirals on the recurrence of hepatocellular carcinoma: The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts)»

Philippe Kolly, Jean-François Dufour

PII: S0168-8278(16)30402-0
DOI: http://dx.doi.org/10.1016/j.jhep.2016.07.032
Reference: JHEPAT 6212

To appear in: *Journal of Hepatology*

Received Date: 10 July 2016
Accepted Date: 13 July 2016

Please cite this article as: Kolly, P., Dufour, J-F., Reply to «Lack of evidence of an effect of Direct Acting Antivirals on the recurrence of hepatocellular carcinoma: The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts)», *Journal of Hepatology* (2016), doi: http://dx.doi.org/10.1016/j.jhep.2016.07.032

Reply to «Lack of evidence of an effect of Direct Acting Antivirals on the recurrence of hepatocellular carcinoma: The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts)»

Philippe Kolly[1,2], Jean-François Dufour[1,2]

[1]Hepatology, Department of Clinical Research, University of Bern, Bern, Switzerland

[2]University Clinic for Visceral Surgery and Medicine, Inselspital Bern, Bern, Switzerland

To the Editor:

We read the article from Pol [1] with great interest, as it provides data that support the notion that patients with a history of treated hepatocellular carcinoma (HCC) do not have an increased risk for recurrence when treated with direct-acting antivirals (DAAs). This article follows the investigations from Reig *et al.* and Buonfiglioli *et al.*, who reported an unexpected early HCC recurrence in patients treated with DAAs [2, 3]. Reig *et al.* noted this trend to be increased when the DAA treatment was taken in the 4 months following HCC treatment, which makes this particular time frame of most interest. These analyses have limitations as acknowledged by the authors themselves and as reported by others [4, 5]. Among these are the small number of patients and the absence of comparison arms. However, it was important to publish these findings to alert other centers to investigate this issue.

In the current state of knowledge, this important issue remains unclear and well-designed studies with proper comparison arms are required to determine the effect of DAAs on HCC recurrence. For this purpose, Pol used three French cohorts to investigate the effect of DAAs on HCC recurrence. The HEPATHER cohort provided the opportunity to study a significantly larger group of patients who were HCV-infected with a history of treated HCC (n=267) than previously published; of whom, 189 had been treated with a DAA. The author found no difference in HCC recurrence rates between treated and untreated patients with DAAs. In our opinion, some points merit further comment.

Almost two-thirds of the cohort were diagnosed with HCC more than 1 year before inclusion in the cohort (65.5% [n=175] >1 year; 34.8% [n=93] >3 years). As the analysis only began at the time of inclusion in the cohort, the study misses – for most of the patients – the particular time frame, identified by Reig *et al.*, at which patients seem to be at risk for HCC recurrence. This may lead to potential underestimation of recurrences in the treated group. Furthermore, it has the potential to lower the rate of HCC recurrence by ignoring patients who had HCC recurrence and died before inclusion, since these patients were specifically excluded from the cohort.

In the survival analysis (Figure 1 of the article), it seems that the whole cohort is included in the untreated group, and that patients were censored as they received DAA treatment. This methodology may artificially decrease the rate of HCC recurrence that arises in patients not receiving DAA therapy.

Finally, the information given about the radiological assessment of the liver is limited. It would be very interesting to know what the delay was between the last radiological assessment and the beginning of DAA treatment.

We congratulate Pol for providing further information about the important issue of HCC recurrence after DAA therapy. We believe that the message may be stronger if the above points could be clarified.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Pol S. Lack of evidence of an effect of Direct Acting Antivirals on the recurrence of hepatocellular carcinoma: The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts). J Hepatol 2016. [Epub ahead of print].

[2] Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. J Hepatol 2016. [Epub ahead of print].

[3] Buonfiglioli F, Conti F, Andreone P, Crespi C, Foschi F, Lenzi M, et al. Development of hepatocellular carcinoma in hcv cirrhotic patients treated with direct acting antivirals. J Hepatol 2016;62(S2):LBP506.

[4] Torres HA, Vauthey J-N, Economides MP, Mahale P, Kaseb A. Hepatocellular carcinoma recurrence after treatment with direct-acting antivirals: First, do no harm by withdrawing treatment. J Hepatol 2016. [Epub ahead of print].

[5] Cammà C, Cabibbo G, Craxì A. Direct antiviral agents and risk for HCC early recurrence: much ado about nothing. J Hepatol 2016. [Epub ahead of print].